



Visual Impairment/Intracranial Pressure Research Clinical Advisory Panel (RCAP) Meeting

Summary Report

December 1, 2014

I. INTRODUCTION

The Visual Impairment/Intracranial Pressure (VIIP) Research and Clinical Advisory Panel convened on December 1, 2014 at the ISS Conference Facility in Houston. The panel members were provided updates to the current clinical cases and treatment plans along with the latest research activities (<http://humanresearchroadmap.nasa.gov/Risks/?i=105>) and preliminary study results. The following is a summary of this meeting.

II. ATTENDEES

RCAP Members

1. **David Baskin, M.D.** - Methodist Hospital; Houston, TX
2. **Conrad Johanson, Ph.D.** - Brown Medical School; Providence, Rhode Island
3. **Byron Lam, M.D.** – Bascom Palmer Eye Institute; Miami, Florida
4. **Andrew Lee, M.D.** - Methodist Hospital; Houston, TX
5. **J.D. Polk, D.O., M.S., M.M.M., C.P.E.** - College of Osteopathic Medicine, Des Moines University; Des Moines, Iowa
6. **Harold Rekate, M.D.** - North Shore Long Island Jewish Health System; Great Neck, NY
7. **Prem Subramanian, M.D., Ph.D.** - Wilmer Eye Institute, Johns Hopkins University School of Medicine; Baltimore, MD

Participants

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|---------------------------------|-----------------------------|--------------------------------|
| 1. Patricia Bahr | 15. Steve Hart | 29. Bradley Rhodes |
| 2. Yael Barr | 16. Janet Kavandi | 30. Graham Scott |
| 3. Michael Barratt | 17. Steven Laurie | 31. Scott Smith |
| 4. David Baumann | 18. Justin Lawley | 32. Jeffrey Sutton |
| 5. Eric Bershad | 19. Tom Mader | 33. Terrance Taddeo |
| 6. Rachel Brady | 20. Sara Mason | 34. William Tarver |
| 7. Jon Clark | 21. Shannan Moynihan | 35. Wafa Tayim |
| 8. Ronita Cromwell | 22. Lealem Mulugeta | 36. Mary Van Baalen |
| 9. Jeffrey Davis | 23. Peter Norsk | 37. Jennifer Villarreal |
| 10. Dorit Donoviel | 24. Christian Otto | 38. Sharmi Watkins |
| 11. Doug Ebert | 25. Nimesh Patel | 39. Mary Wear |
| 12. Millennia Foy | 26. Ashot Sargsyan | 40. Jimmy Wu |
| 13. David Francisco | 27. Mark Shelhamer | |
| 14. Charles (Bob) Gibson | 28. Michael Stenger | |

III. MEETING AGENDA

Time	Topic	Presenter(s)
8:30	Welcome and Introductions	<i>Dr. Jeff Davis</i> <i>Jennifer Villarreal</i>
8:45	Latest case review	<i>Thomas Mader</i>
9:15	Ocular Health flight study preliminary data	<i>Christian Otto</i>
9:45	New clinical practice guideline overview	<i>Shannan Moynihan</i>
10:15	<i>Break</i>	
10:45	Changes to Medical Requirements (MRID) testing	<i>Steve Hart</i>
11:15	Pre/post flight lumbar puncture MRID	<i>Bill Tarver</i>
11:45	<i>Lunch</i>	
12:00	Lunch Speaker: Invasive Telemetric ICP Monitoring	<i>Christian Otto</i>
12:30	Clinical treatment/data review	<i>Shannan Moynihan</i>
1:00	Russian implementation and data comparability	<i>Jimmy Wu</i>
1:30	1-Carbon study results	<i>Scott Smith</i>
2:00	Microgravity ICP on Zero-G plane	<i>Justin Lawley</i>
2:30	Cardiac profile data	<i>Christian Otto</i>
3:00	<i>Break</i>	
3:15	Retrospective OCT analysis	<i>Nimesh Patel</i>
3:45	Discussion and recommendations	<i>All</i>
5:00	<i>Action Summary & Adjourn</i>	<i>Jennifer Villarreal</i>

IV. KEY DISCUSSION POINTS

The following topics were presented to and discussed by the panel. The comments and recommendations summarized below do not necessarily represent the unanimous opinion of the panel.

OCT related comments/recommendations

- OCT analysis was presented and discussed. A potential relationship between the size of the Bruch's Membrane Opening (BMO) area and RNFL thickening was noted, such that larger optic nerves have bigger RNFL changes.
- Evaluate anterior segment via Optical Coherence Tomography (OCT). The volume of the choroid increases inflight, without a concomitant increase in IOP. This means that another volume within the eye is decreasing, possibly that of the anterior chamber, due to a decrease in aqueous humor production. A decrease in anterior chamber volume would move the lens forward and increase myopia, which has not been seen in crewmembers. However, this does not rule out the possibility that the magnitude of previously reported hyperopic shifts may have been lessened somewhat by this slight increase in myopia. Since even a slight narrowing of the anterior chamber could put some pre-disposed astronauts at risk for angle closure glaucoma this potential anatomic change should be investigated. This can be evaluated with the addition of anterior segment OCT. Note: NASA's "Fluid Shifts" flight research study includes measurement of this parameter.
- Consider OCT angiogram/venogram software to measure venous engorgement/venous outflow. Optic nerve sheath (ONS) distention places anterior pressure on the globe, causing choroidal folds, but the choroidal folds could also be secondary to choroidal congestion.
- Consider evaluating space-naïve, high performance pilots, with OCT and other technologies, to obtain measurements of the choroid, RNFL, peripapillary total retinal volume, ONSD, etc.
- Consider getting corneal topography on crewmembers pre-, in- and postflight. Note: Currently we collect keratometry data using the IOL Master, not corneal topography. (IOL = IntraOcular Lens)
- Consider looking at the ganglion cell layer at the macula/fovea, as well as measuring the choroidal thickness at the macula. At present we have limited macular data. Most OCT data is peri-macular.
- Use OCT preflight to look at the lamina cribrosa position and structure as well as peripapillary total retinal volume.
- Look at OCT-MRW (Minimum Rim Width) post fenestration of IIH-ICP patients to inform us whether fenestration is a viable therapy in the future for Mars missions, etc.

- Get OCT on Skylab and Shuttle-Mir astronauts to evaluate for permanent residual structural changes (choroidal striae, scarring) from previous long duration flight.
- Considerable progress has been made on understanding the nature of the retinal fiber layer damage in long duration flights. The high tech OCT on orbit has proven valuable for delineating the fine structural damage in the back of the eye and optic nerve head. This should help to devise treatment strategies for pin-pointing targets to pharmacologically minimize pathology and loss of visual functions.

Ultrasound and MRI related comments/recommendations

- Evaluate venous outflow, the subarachnoid fluid around the sheath, and the distribution of the CSF by quantitative MRI. In Alperin's IIH MRI study he found an increase in the volume of extraventricular intracranial CSF volume in IIH patients. Note: An existing NASA grant includes these parameters. Results should be available by the next RCAP meeting.
- Consider in-flight imaging of transverse sinus morphology. In non-obese IIH patients, changes in the transverse sinus geometry are common and they reverse when pressure is lowered with an LP. Note: Ultrasound (U/S) imaging is limited to the deep vein of Rosenthal.
- Consider evaluation of eye morphology/geometry. It is unknown if the globe shortening is due to the eye getting smaller, or if concurrently the geometry of the eye is changing so that the height increases to compensate for the axial shortening. We only measure axial length (Anterior-posterior diameter), not globe height. Notes: There is an MRI technique that can evaluate 3D globe morphology. A 3D volumetric ultrasound is in development by Dr. Dentinger in collaboration with General Electric under an NSBRI funded grant. Reference <http://www.nsbri.org/projects/indivProject.asp?id=440&projID=311>
- Investigate the nature of optic nerve sheath diameter change - permanence, elasticity, ultrastructure.
- Sequestration of CSF in the optic nerve sheath - Measure the anatomical structure of the optic nerve sheath complex on the preflight MRI and compare these findings to post mission measurements.
- Consider evaluation of eye vessel diameters – At present the resolution of U/S only allows visualization of flow velocity but cannot visualize the vessel itself. However, it is the actual vessel diameters that are important. The RCAP members noted that flow velocity is not used clinically because it is only a surrogate to flow, which is a surrogate to diameter.
- Mathematical models are needed to evaluate the correlations between findings, to determine which measurements and tests best predict outcome measures, and to prioritize which clinical/research tests are of most value. Note: Modeling is underway in NASA's Digital Astronaut project and

external collaborations funded by NSBRI. Reference
<http://humanresearchroadmap.nasa.gov/Gaps/?i=576> and
<http://www.nsbri.org/projects/indivProject.asp?id=358&projID=327> .

- The MRI technique to calculate CSF production rate is flawed and prone to error because the total volume of each pulse is so much higher than the net flow. Two RCAP members noted that CSF formation rate does not change over a large range of ICP values. Formation rate could change with a medication such as Diamox, but not secondary to increased or decreased pressure. In addition, as long as the CSF absorption is the same, an increase in CSF production postflight will not increase ICP. Another RCAP member noted that there is anatomical evidence from rats that supports decreased CSF formation in-flight and increased CSF formation postflight. The hypothesized mechanism: Increased ICP decreases the perfusion pressure in the choroid plexus capillaries, leading to less blood flow, less filtration, and less CSF production. Also could be secondary to changing levels of ANP or its receptors.
- Consider characterizing the structural or secondary complications of the increased volume in the choroid using a 7.1 Tesla MRI. Consider pre/postflight 7.1 Tesla MRI of the eye and ONSD with eye coils.
- Consider using a 7.1 Tesla MRI to evaluate the arachnoid villi for damage that may be secondary to increased venous pressure and loss of venous hydrostatic gradient.
- In MRI analyses by Dr. Donna Roberts (NASA grant), blood-brain permeability to gadolinium could be assessed to explore the status of the brain capillaries in spaceflight.
- The ability of MRI to measure compliance is an important step forward. Recommend extensively pursuing these compliance measurements in astronauts via MRI.

Treatment comments/recommendations

- Consider being more aggressive with in-flight treatment of cases. The RCAP's assumption until now was that in the mild cases we can just watch and see, but we now see a case that was mild in-flight and yet postflight they are not improving or even worsening, so perhaps earlier intervention is warranted.
- Several panelists agreed that the treatment protocol should follow visual fields and not visual acuity, as the visual acuity changes are refractive in nature, and terrestrial standard of care is to monitor with visual fields. Several felt that visual acuity should not be used for high stakes decisions like "de-orbit" because of low sensitivity and low specificity (e.g. loss of acuity might be refractive shift and normal acuity can occur in papilledema with severe visual loss).

- Develop visual field technology for mission use.
- Treatment with Diamox in-flight might make the translaminal pressure worse by decreasing the IOP. If IOP is slightly increased in-flight that may be protective against worse disc edema. Lowering IOP is almost certainly a bad idea. Consider an in-flight study with Diamox administration (2 grams daily, for 3 days) to evaluate what happened to IOP and OCT parameters. Give for 72 hours in-flight. While this is a large dose, it will be given for a short period of time.

Another RCAP member suggested that we consider one 500 mg sequel BID as the dose, and reasoned that since Diamox has never been given previously during chronic microgravity exposure, it might be appropriate to get baseline IOP and OCT measurements just prior to starting this medication and then every 12 hours during the 3 days to observe possible changes in disc morphology. If there was a pre-existing increase in optic nerve sheath pressure, from compartment syndrome, Diamox would decrease IOP but may have little if any effect on the ON sheath pressure. This could lead to a prominent pressure differential across the lamina cribrosa that could cause a sudden increase in disc edema. We have to be prepared to stop this medication if an increase in disc edema were to occur.

- Consider preflight optic nerve fenestration as a preventative measure prior to an extra-long duration mission (such as a 1-year mission to the ISS or a longer mission to Mars). The RCAP members had differing opinions on this, with some quoting a high early failure rate and a very high complication rate, and making the point that since we don't understand the etiology of VIIP, it is premature to attempt preventive measures that are so invasive and high-risk.
- Identify prophylactic agents to minimize damage to ganglion cells/ RNFL in spaceflight.
- Consider potential pharmacologic agents to unload central venous volume (pressure) increased by microgravity. Strategies to reduce augmented central venous volume in spaceflight may be important in attaining greater effectiveness of CSF formation-inhibiting (or CSF reabsorption-enhancing) agents. To lower ICP, the use of more than one pharmacologic agent (or therapeutic modality) may be necessary to mobilize CSF, brain interstitial fluid, and central venous blood that are not being efficiently cleared from the intracranial and extracranial spaces.
- Evaluate agents to reduce formation of CSF, and whether there are agents better than acetazolamide (Diamox) to control ICP.

ICP measurement comments/recommendations

- Most panelists agreed that ICP data is needed urgently. At least one expressed that it is unethical to send people on longer missions without understanding the risk to their health. This may be accomplished with a pre and postflight LP combined on all crewmembers with noninvasive pre/post measurement and noninvasive in-flight, or with implanted ICP probes (3-4 crewmembers

would be sufficient to establish proof of concept). Ideally, LP would be done on all crewmembers pre- and postflight. LP can be done 6-12 months preflight, but postflight needs to occur as soon as possible after landing, preferably on the first day back on Earth.

- Lumbar CSF composition can yield considerable information about the state of the choroid plexus (an influential player in CSF dynamics) as well as brain metabolism and viability. As the biomedical literature continually provides new insights on CSF neurochemistry, it is prudent to add analytes to astronaut CSF samples. Dr. Harold Rekate is able to analyze CSF samples for multiple novel biomarkers (6 cc of CSF will allow a full battery, although 1 cc can be sufficient for multiple tests, because of microliter analysis methods). Do both proteomics and metabolomics – look wide and then narrow the list. Add a test for level of melatonin in the CSF.
- Consider analyzing frozen CSF samples previously collected from crewmembers for these biomarkers. However, the samples may not have been frozen in a way that is conducive to such analysis (i.e. potentially not snap frozen in liquid nitrogen). Future samples should be frozen immediately in liquid nitrogen. Dr. Rekate will send Dr. Tarver the recommended freezing protocol for CSF.
- Assess aquaporin 1 and 4 levels in CSF, pre-(control) and postflight, as a gauge of possible choroid plexus injury. AQP1 resides in the apical (CSF-facing) membrane of choroid plexus. Damage to the plexus (from radiation, gross ventricular fluid shifts in rats in Shuttle flights, etc.) might elevate AQP1 in CSF. AQP1 is uniquely a marker for choroid plexus, since it is not normally expressed in any other region in the CNS. By analogy, any AQP4 found in CSF would likely reflect pathophysiology to the ventricular wall, as is the case when AQP4-containing ependymal cells are damaged (stripped) in hydrocephalus. Maintaining the structural integrity of the CSF-bordering plexus and ependyma is essential for balancing fluid movements, and pressure gradients, between ventricles and brain.
- Measure retinol (elevated 10-fold in terrestrial IHH) in astronauts to ascertain possible similar disruptions in the linkage of retinoid metabolism to CSF dynamics at arachnoidal drainage sites. Carrier RNP, and retinol, the substrate it binds, are normally present at certain levels and ratios, both in serum and CSF. Disturbances in vitamin A (retinoid) metabolism in some IHH patients causes a stoichiometric imbalance in RNP to retinol, i.e. possibly reflecting disorders in CSF reabsorption across the arachnoid membrane.
- Six of eight panelists recommended implantable telemetric ICP probes for obtaining continuous ICP measurement in crewmembers. One expert panel member states that the risk of implanting the Raumedic device in normal subjects is very low and the risk of things like seizures or intracranial bleeding is very low (0.5% in skilled hands). The risk noted in the literature (of hydrocephalic and very ill patients) is about 1 in 85 – quite significant but most likely not what we would see in healthy astronauts. The seizure rate noted for the hydrocephalic patients could be that high in this group of

patients, even without probe implantation. Most RCAP members felt that the risk for peri-probe edema would not be higher due to spaceflight/fluid shifts. The probe would be implanted months before the mission, and any edema would resolve within weeks. RCAP members noted that if such probes will be used on crew, it would help advance care for thousands of patients in the U.S. since there is not sufficient impetus to conduct studies and get this FDA approved. However, from the practical perspective of flight operations, if the implanted crewmember complains of headache or fever onboard, NASA flight surgeons would have no choice but to deorbit, due to lack of on-board resources to rule out complication from the implant. That risk to the mission, and consequently NASA's space program, may not be acceptable. However, RCAP members noted that the flight will occur several months after implantation, when a complication is very unlikely. The ethics of placing an invasive probe in a healthy person's brain were also discussed. One RCAP member felt that the risk to the astronauts, mission and space program outweighs the need to know.

- Using a transducer in the subdural intracranial of lumbar space was discussed. While a lumbar transducer would be safer, the results would be hard to interpret. The telemetric probe is not compatible with lumbar insertion, because it is stiff, would touch nerves and be painful. The smaller flexible probes that could be used are not telemetric, which would limit their utility (extension through the skin increases infection risk, so these can be used only for a short period of time). A subdural probe usually ends up in the brain. Placing a probe in the cisterna magna is riskier than placing an intraparenchymal probe.
- Consider flying to space an animal model (such as a primate) instrumented with the telemetric probe, or an instrumented patient on a "Make a Wish" type mission (as a tourist).

Epidemiology, etiological hypotheses, and risk factor comments/recommendations

- There were differing opinions among the RCAP members as to the etiological mechanisms underlying VIIP, with some supporting increased ICP as the leading mechanism and others supporting an eye/orbit/optic nerve centered mechanism (such as optic nerve compartment syndrome) with normal or slightly elevated ICP. It was recognized that the different theories are not mutually exclusive, and that the etiology might be multifactorial.
- Data from Russian cosmonauts and USOS astronauts can be analyzed both separately or combined, while adjusting for gender, age, lifestyle, and other parameters.
- Hyperhomocysteinemia is a known risk factor in men with terrestrial IIH. The thought is that these patients have a low level of thrombophilia, leading to partial venous outflow obstruction (look for papers by Gluck et al). The homocysteine levels in that IIH population are slightly higher than in the astronaut population (about 16 mmol). There is a different distribution of these genes in Russians, so would be interesting to evaluate in the cosmonauts. This could explain the cotton wool

spots, and could also explain the gender difference in VIP incidence (as these polymorphisms tend to occur in males).

The role of 1-C polymorphisms needs expansion and the mechanism of the pathophysiology needs to be identified. It was also suggested that 1-C polymorphisms, blood levels of homocysteine, and their correlation to ICP and papilledema be evaluated in IIH patients.

- Treating with folate or other vitamins (B6 and B12), while it brings the homocysteine levels down, does not reduce the risk of thrombophilia. However, since such treatment is low risk, it may be an option to try in affected crewmembers.
- Patients with strokes also have a higher likelihood of high homocysteine and the question whether crew MRIs show any small vessel disease was discussed. While anecdotally some crewmembers have had punctate findings on MRI, no significant, or VIIP relationship has been noted to date. A re-evaluation of these MRIs was suggested.
- An RCAP member also suggested measuring 1-C metabolites (homocysteine, cystathionine and 2MCA) in CSF of astronauts with polymorphisms vs. controls. These metabolites might be especially toxic to the retina and optic nerve if allowed to build up in blind cul-de-sacs of CSF. In addition, it was suggested that CSF samples from the subarachnoid space around the optic nerve might be collected and analyzed from IIH patients with and without the 1-C polymorphisms while they undergo optic nerve fenestration analyzed in IIH patients.
- A recent zero-G study showed a decrease of ICP compared with supine measurements on the ground. Bed rest studies from the same group showed an increase in ICP with a return to supine levels after 3-24 hours of 6 degrees head-down tilt, with no elevation of ICP with 5 minutes of 0.7% CO₂ exposure. It was noted that it may take higher levels of CO₂ to cause a significant increase to ICP – it is not a linear relationship. CO₂ levels on ISS are 10X terrestrial levels. Expired CO₂ levels were found to be 39.0 mmHg in 10 subjects, vs 36.7 mmHg preflight in the standing position (p<0.05). RCAP members questioned whether the patient population used (Ommaya reservoir patients) should be considered as having a “normal” central nervous system. The brief nature of the microgravity exposure on the parabolic plane was a concern to the RCAP members. However, other parameters (such as CVP) measured in the past during parabolic flights were later corroborated when measured during spaceflight. Unloading of the thorax during microgravity was speculated to underlie the decrease in absolute CVP and ICP in comparison to their supine ground level. This is in contrast to the 24 hour mean microgravity CVP and ICP which appear to be elevated above the mean 24 hour ground levels.
- Segregate the data for those who are repeat fliers vs. those who were spaceflight naïve. Crewmembers who fly more than once could be considered in a separate category, because they may be predisposed to VIIP.

- Consider methods to measure orbital compartment pressure. In terrestrial IHH, within 2-3 weeks of lowering the ICP the disc edema resolves. However, in crewmembers the disc edema persists beyond normalization of the ICP, which supports that there could be scarring/structural changes to the eye, or continued localized pressure in the optic nerve sheath or the orbit.
- Analyze systematically changes in CSF, brain and venous compliance; and ascertain factors affecting the compliance parameter in astronauts (state of fitness, anatomical variations, genetic predispositions, etc.) Changing values of tissue, vascular and CSF compliance in microgravity are properties that deserve more attention in explaining the pathophysiology of intracranial fluid imbalance in spaceflight. Look at scleral compliance (biometrics) as well.
- Continue CO₂ studies. Consider studies that experimentally alter CO₂ during spaceflight with a breathing device.
- Consider the role of radiation and difference in high LET (linear energy transfer) with VIIP.
- An RCAP member questioned the value of bedrest studies to reproduce any of the changes seen with VIIP and suggested that inversion studies, even short-term, will give us a better idea of the shifts in fluids as well as forces being exerted in the microgravity environment. Combining exposures in the experimental models (CO₂ + positioning; exercise + CO₂ + inversion) may at first glance introduce too many variables, but it could have the best chance in the short term for identifying countermeasures.
- Any VIIP-related testing postflight needs to occur as close to landing as possible (i.e. within a few to several days). Although done as quickly as practically possible, this is somewhat problematic in that homeostatic adjustments (microgravity back to 1G) in ICP and CSF formation can occur rapidly (neuroendocrine adaptations, e.g. ANP, within hours to a few days).
- Consider the effects of re-entry deceleration on the pathophysiological status early postflight. Adding another layer of complexity to the assessment of pathophysiology and homeostatic rebound (or not) are the physical stressors, on fluid redistribution and pressure, caused by the reentry deceleration involving several G forces. It is possible that some of the physiological damage (possibly displaying hysteresis), on the delicate microarchitecture of the trabeculae in the subarachnoid space, occurs mainly in the stressful deceleration when returning to earth.

V. CONCLUSION

NASA extends its sincere appreciation to the distinguished panel members who have dedicated many hours of intellectual research and debate to assist NASA with this critical risk. NASA will deliberately consider the advice of our esteemed panel members and implement the recommendations where

possible and practical. We also thank the extended team of scientists, physicians, and engineers who have made great strides towards elucidating the etiology behind the VIIP syndrome and potential mitigating countermeasures.